# Papers and Articles

# Bovine spongiform encephalopathy: Epidemiological studies

J. W. Wilesmith, G. A. H. Wells, M. P. Cranwell, J. B. M. Ryan

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**This study, initiated in June 1987, describes the epidemiology of bovine spongiform encephalopathy (BSE), a recently described novel neurological disease of domestic cattle first identified in Great Britain in November 1986. Records suggested that the earliest suspected cases occurred in April 1985. There was variability in the presenting signs and the disease course, but the majority of cases developed behavioural disorders, gait ataxia, paresis and loss of bodyweight; pruritus was not a predominant sign. The form of the epidemic was typical of an extended common source in which all affected animals were index cases. The use of therapeutic or agricultural chemicals on affected farms presented no common factors. Specific genetic analyses eliminated BSE from being exclusively determined by simple mendelian inheritance. Neither was there any evidence that it was introduced into Great Britain by imported cattle or semen. The study supports previous evidence of aetiological similarities between BSE and scrapie of sheep. The findings were consistent with exposure of cattle to a scrapie-like agent, via cattle feedstuffs containing ruminant-derived protein. It is suggested that exposure began in 1981/82 and that the majority of affected animals became infected in calfhood.**

IN October 1987, Wells and others reported the occurrence of a novel neurological disease of domestic cattle in southern England which has close similarities to natural scrapie of sheep and related transmissible spongiform encephalopathies. The disease was accorded the name bovine spongiform encephalopathy (BSE). The initial cases were diagnosed by histopathological examination in November 1986, and by June 1987 the reported incidence required an epidemiological investigation. This paper describes the results of the initial studies to obtain descriptive epidemiological, including genetic information; to monitor the disease incidence both within herds and nationally; to collect data on the frequency of individual clinical signs and the duration of the disease; and to develop aetiological hypotheses.

## *Case finding*

Information on cases of BSE was obtained when suspect clinical incidents were reported by veterinary surgeons to Ministry of Agriculture, Fisheries and Food (MAFF) veterinary investigation (VI) centres as a result of a nationwide request initiated in June 1987 for the voluntary notification of previous and current cases.

## *Case definition*

Confirmed cases were defined as those in which histopathological examination of the brain revealed a spongiform encephalopathy, consistent in all major respects with that previously described (Wells and others 1987).

Clinically suspect cases were defined as those which on clinical examination presented a syndrome consistent with, or having significant features of, the original descriptions of signs exhibited by animals shown to have the neuropathological changes of confirmed cases (Wells and others 1987, Cranwell and others 1988, Gilmour and others 1988), but on which no neuropathological examination was conducted.

All 'cases' of BSE refer to the summation of confirmed and clinically suspect cases.

## *Collection of data*

A questionnaire was used to obtain epidemiological data from herds with at least one confirmed case. This provided the following details relating to cases: date of birth; breed; sex; the herd of origin of the animal if purchased; the date of clinical onset and stage of pregnancy at onset; the pedigree of the animal when known; the identities of offspring, retained and intended to be retained in the adult herd, and of siblings with the same dam as the case retained in the adult herd. The presence or absence of specific clinical signs, previously established in confirmed cases also original histories and clinical observations were recorded for each case. Specific descriptions of the presenting signs and progession of the disease were also obtained from the herdsman and veterinary surgeon.

In addition, the following data relating to the herd were obtained: herd type; adult herd size and age structure; the presence of sheep on the farm since 1980; the destination of animals sold and the origin of breeding animals since the birth of the initial case, and details of the use of therapeutic pharmaceutical products, vaccines, pesticides and herbicides. Feeding practices since the birth of the initial case were also determined.

The initial questionnaire was modified in December 1987, when data had been accumulated from 192 herds. The modified questionnaire continues to obtain information from affected herds.

The data on the pedigrees of affected animals obtained from farm records were supplemented and extended by reference to breed society herd books and records.

Herd breeding records, from 1967 to June 1987, were abstracted for one multiple case herd to facilitate retrospective genetic analyses. These records comprised the identity of the females born in the herd during this period, their date of birth, the identities of their dam and sire and their date of death, or departure from the herd.

Numbers of herds at risk for the calculation of herd incidence rates and herd size distribution, were obtained from results of the June 1986 agricultural censuses in England, Wales and Scotland (MAFF, DAFS, unpublished statistics).

To examine the association between clinical onset and stage of pregnancy, the monthly calving distributions were obtained from a previous study of some 250 dairy herds in England and Wales (Wilesmith and others 1986).

**J. W. Wilesmith**, BVSc, MRCVS, **J. B. M Ryan**, BEd, MiBiol, Epidermiology Unit, **G. A. H. Wells**, BVetMed, MRCVS, Pathology Department, Central Veterinary Laboratory, New Haw, Weybridge, Surrey, KT15 3NB

**M. P. Cranwell**, BA, VetMB, MRCVS, Veterinary Investigation Centre, Staplake Mount, Starcross, Exeter, Devon

*Analyses of data*

Data collected by means of the questionnaires were subjected to conventional epidemiological analyses to provide a quantitative epidemiological description of the disease. The data analysed and presented refer to all cases whose date of clinical onset was before April 1, 1988, unless otherwise specified.

A computer simulation model was constructed, on the hypothesis that BSE is caused by a transmissible agent, to examine the time of onset and duration of exposure, the incubation period distribution and age classes of animals exposed. The model consisted of a large population of calves, young stock and adults; the latter were subjected to age specific culling rates obtained from previous studies of dairy herds (J. W. Wilesmith and J. B. M. Ryan, unpublished observations). Values for the exposure parameters and incubation period were imposed on the model. The incubation period was assumed to have a log normal distribution, and to exhibit no variation with age at first exposure. The age specific incidences of BSE in herds with confirmed cases during 1987 were used to assess the validity of the exposure and incubation period parameters. The simulation was also used to predict changes in age specific incidences in future years.

The complete herd breeding records obtained from the multiple case herd were analysed to examine the hypothesis that BSE is the result of an autosomal mode of inheritance. For this, the pedigrees of all confirmed cases in Great Britain, accumulated by the end of March 1988, were used to produce a list of putative heterozygous carrier bulls, ie, the sires or maternal grandsires of confirmed cases. This allowed the identification of animals from the specified herd whose sire and maternal grandsire were putative heterozygous carriers. Only confirmed cases were considered in the analysis of the segregation ratio of unaffected : affected cases in this herd.

## Results

The frequency of the presenting clinical signs recorded for 156 confirmed cases is shown in Fig 1. The most common history given by the herdsmen was 'nervousness' or altered behaviour and, or, temperament. Manifestations of such 'nervous' behaviour included a reluctance to enter the milking parlour or pass through other doorways, separation from the rest of the herd at grass, apprehension and hyperaesthesias, particularly uncharacteristically vigorous kicking in response to handling at milking. Subtle changes in pelvic limb gait, reported by herdsmen, were the earliest locomotor signs to be recognised in some cases. In others the first sign of abnormality was difficulty in rising from a normal lying posture, but on careful inspection this weakness was invariably associated with pelvic limb ataxia. The majority of such cases were dry cows at grass and were not examined each day.

Clinical examinations revealed neurological and general signs; no results of clinical neurological testing were available. These reported observations were, where possible, interpreted and assigned to conventionally accepted categories of the neurological examination. The frequencies of signs of altered mental status, posture or movement, and sensation in the initial 192 confirmed cases are shown in Fig 2. Deficits were recorded for 97·9 per cent, 92·8 per cent and 94·9 per cent, in each of these three categories respectively, and in all three categories for 87·2 per cent of the 192 cases. General clinical signs in this set were loss of bodily condition (77·6 per cent), liveweight loss (73·4 per cent) and reduced milk yield (69·8 per cent). In 78·6 per cent of animals each of the neurological sign categories and at least one of the general signs were represented at some stage of the observed clinical course. No cases exhibited only general signs. The range and severity of the clinical signs progressed in all cases. Initial subtle gait abnormality progressed to an obvious swaying gait, shortened stride and awkwardness in turning. Day to day variations in the presence and intensity of signs were observed, and maintaining animals in quiet and familiar surroundings resulted in a reduction in the severity of signs, particularly hyperaesthesia. Appetite was maintained in all but seven (3·6 per cent) cases and apparent difficulty in prehension was observed in a further five (2·6 per cent) cases. Other clinical signs recorded at a similar or lower frequency were a reluctance to mount steps, exophthalmos, moaning/vocalising, intraspecific

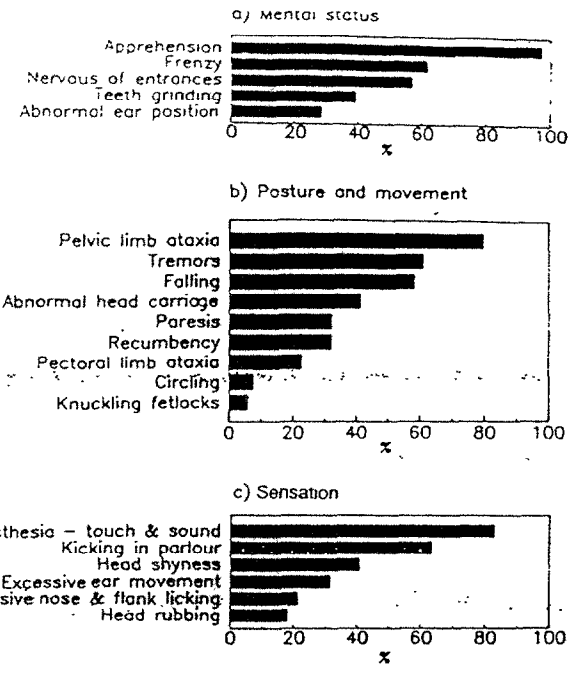


FIG 2: Percentage distribution of frequency of observational neurological signs in 192 confirmed cases of BSE

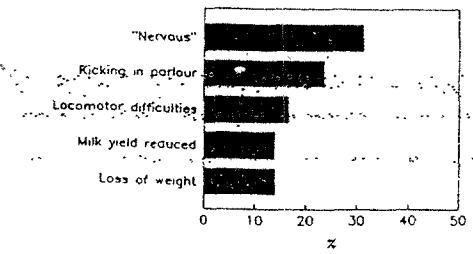


FIG 1: Percentage distribution of 156 confirmed cases of BSE by the reported presenting clinical signs

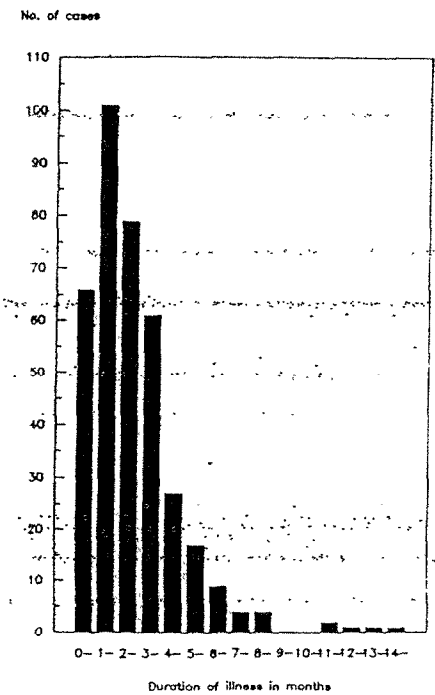


FIG 3: Distribution of confirmed cases by duration of illness

TABLE 1: Clinical histories of seven confirmed cases of BSE with a duration of illness of less than 15 days

| Case | Clinical history | Duration of illness (days) | Died/ slaughtered |
|---|---|---|---|
| 1 | Initial hypermetric gait, progressive ataxia over next three days followed by 'nervous signs' and recumbency | 7 | Slaughtered |
| 2 | Rapid loss of weight and 'became dangerous' | 11 | Slaughtered |
| 3 | Rapid deterioration after simultaneous onset of pelvic limb ataxia and 'nervousness' with recumbency 10 days after onset | 11 | Died |
| 4 | Acute reduction in milk yield and loss of weight followed by aggression and recumbency | 11 | Slaughtered |
| 5 | Rapid deterioration in gait resulting in falling and inability to walk on concrete | 12 | Slaughtered |
| 6 | Initial vocalising followed by recumbency 10 days after onset | 12 | Slaughtered |
| 7 | Paraparesis culminating in recumbency | 14 | Slaughtered |

agonistic behaviour, salivation, seizures, lachrymation, reluctance to lie, licking of objects and scratching of the head with a hind foot. Signs of severe pruritus were not evident but a reflex resembling that of the 'nibbling' reflex of scrapie-affected sheep, with neck extension and lip movements, was elicited in a small number of cases by palpating the lumbosacral spine.

The distribution of the duration of illness of all cases, from clinical onset to death or slaughter is shown in Fig 3. The constellation of clinical signs comprising apprehensive behaviour, locomotive deficits, hyperaesthesia and weight loss became apparent in the majority of cases six to eight weeks after onset. Slaughter of affected animals became necessary because of their unmanageable behaviour, traumatic damage as a result of repeated falling and prolonged recumbency; death occurred in seven of the 192 cases. The duration from clinical onset to death or slaughter of 10 of the 192 cases was 14 days or less. Of these, three were slaughtered early in the course of the disease with an established clinical diagnosis. The clinical histories of the remaining seven cases (3·6 per cent) are shown in Table 1.

The distribution of all cases by month and year of onset is shown in Fig 4. Herd records revealed that the earliest clinically suspect cases occurred in April 1985. The incidence increased markedly in September 1987 and thereafter a constant incidence of some 60 cases per month continued until January 1988. Examination of the course of the epidemic after this date is not possible at the time of writing because of the lag between the time of clinical onset and the time of notification.

The percentage incidence of affected dairy herds by county in England, Scotland and Wales since the start of the epidemic is shown in Fig 5. The incidence was greater in the counties of southern England than in the rest of Great Britain, with the greatest reported incidence in Kent.

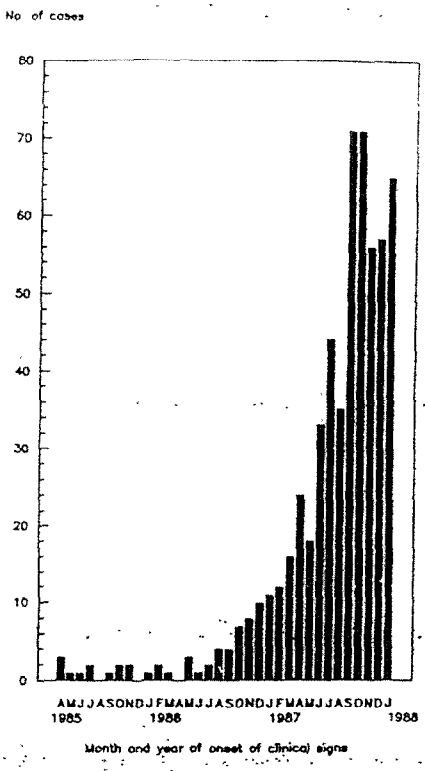


FIG 4: Distribution of cases by month and year of onset

The distribution of cases by functional type (dairy or beef suckler) and by breed is shown in Table 2. This dairy breed distribution is similar to that for England and Wales (Milk Marketing Board 1987) indicating no breed predisposition.

The recorded incidence, from April 1, 1985 to March 31, 1988, of dairy herds affected (311 of 44, 767) was considerably greater than the incidence in beef suckler herds (11 of 54, 166).

All cases were in adult females except for one confirmed and one clinically suspect case in adult males, resulting in a comparable incidence in males and females, given the available denominators from the annual agricultural censuses.

The incidence of affected dairy herds increased with increasing herd size (Table 3). The estimated annual within herd incidence in the 12 month period April 1, 1987 to March 31, 1988 for the herds with at least one confirmed case ranged from 0·20 per cent to 11·11 per cent of adult animals, with a mean of 1·52 per cent. From April 1, 1985 to March 31, 1988, 77·2 per cent of affected herds had experienced only one case. During the same period multiple cases were reported in 128 herds and, in 75 of the 100 herds for which the dates of birth were available, two or more cases were born in the same calving season. The distribution of these herds by the total number of cases and the number of cases born in the same calving season is shown in Table 4.

All cases occurred in adult animals with an age range of two years nine months to 11 years of age. The age specific incidences of BSE within 146 herds which experienced at least one confirmed case in the 12 month period January to December 1987 are shown in Fig 6. These herds comprised 17, 339 animals of two years of age or older and the highest incidence was in the four-year-old age group. A marked reduction in incidence was evident in six-year-old animals (0·25 per cent) compared with five-year-old animals (1·92 per cent). A compari-

**TABLE 2: Distribution of all cases of BSE by breed, and confirmation status**

| Breed | Confirmed cases | | Clinically suspect cases | | All cases | |
|---|---|---|---|---|---|---|
| | Dairy cows | Beef suckler cows | Dairy cows | Beef suckler cows | Dairy cows | Beef suckler cows |
| Friesian / Holstein | 451 | 0 | 211 | 0 | 662 | 0 |
| Ayrshire / 3/4 Ayrshire | 11 | 0 | 0 | 0 | 11 | 0 |
| Guernsey / 3/4 Guernsey | 10 | 0 | 8 | 0 | 18 | 0 |
| Hereford × Friesian | 0 | 10 | 0 | 2 | 0 | 12 |
| Devon × Friesian | 0 | 1 | 0 | 0 | 0 | 1 |
| Jersey × Friesian | 1 | 0 | 0 | 0 | 1 | 0 |
| Shorthorn | 1 | 0 | 0 | 0 | 1 | 0 |
| Shorthorn × Danish red | 1 | 0 | 0 | 0 | 1 | 0 |
| Jersey | 1 | 0 | 1 | 0 | 2 | 0 |
| Charolais | 0 | 1 | 0 | 0 | 0 | 1 |

**TABLE 3: Incidence of affected dairy herds by herd size**

| | Adult herd size | | | |
|---|---|---|---|---|
| | ≤ 50 | 50-99 | 100-199 | ≥ 200 |
| Number of herds at risk | 21,072 | 15,728 | 6935 | 1032 |
| Number of affected dairy herds | 30 | 113 | 134 | 34 |
| Incidence (%) | 0·14 | 0·72 | 1·93 | 3·29 |

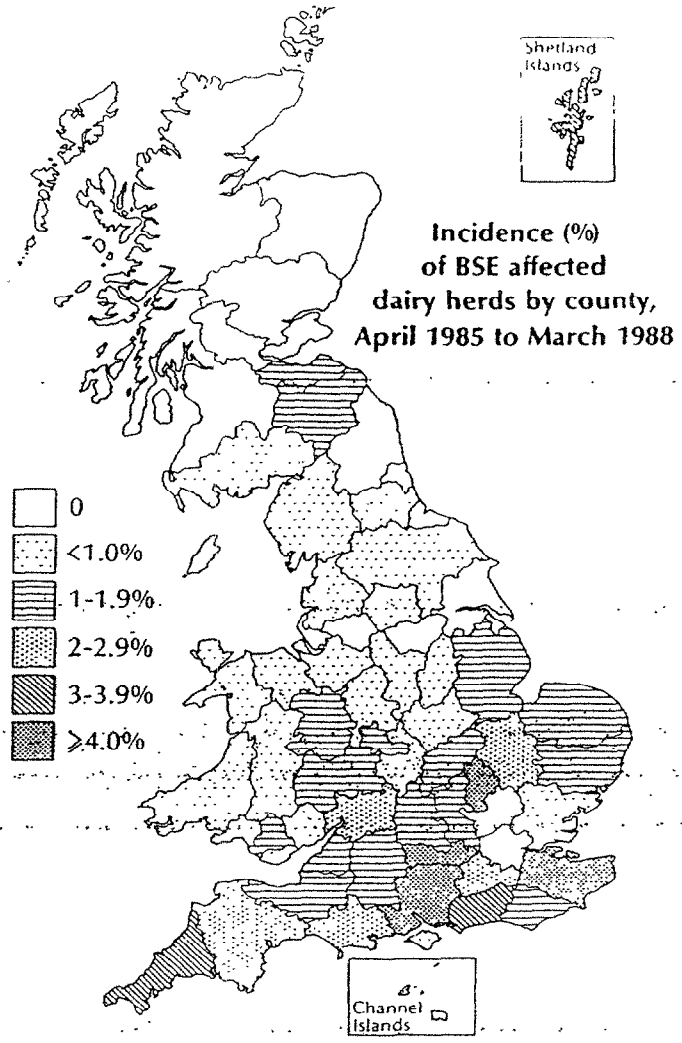


FIG 5: Percentage incidence of BSE affected dairy herds by county, April 1985 to March 1988

son of the percentage distributions of all BSE cases, by year of birth, having a clinical onset in the period January to June 1987 with the same distribution for cases having a clinical onset in the period January to March 1988 showed no evidence of a major change in the age specific incidence rates (Fig 7). There was no evidence of an association between the stage of pregnancy or season and clinical onset.

The distribution of 145 herds, with at least one confirmed case, by their cattle purchasing policy and the presence of sheep on the farm since 1980 is shown in Table 5. In 15 per cent of herds no cattle had been purchased and 20 per cent of herds had had no contact with sheep.

**TABLE 4: Distribution of 100 multiple case herds by the number of cases per herd and the maximum number of cases born in the same calving season**

| Total number of cases per herd | Number of cases born in the same calving season | | | | | | Total |
|---|---|---|---|---|---|---|---|
| | 0 | 2 | 3 | 4 | 5 | 6 | |
| 2 | 24 | 29 | 0 | 0 | 0 | 0 | 53 |
| 3 | 1 | 13 | 7 | 0 | 0 | 0 | 21 |
| 4 | 0 | 6 | 4 | 1 | 0 | 0 | 11 |
| 5 | 0 | 3 | 1 | 0 | 0 | 0 | 4 |
| 6 | 0 | 1 | 2 | 0 | 1 | 1 | 5 |
| 7 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| 8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 9 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| 10 | 0 | 1 | 0 | 1 | 0 | 0 | 2 |
| 11 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| 12 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| Total | 25 | 53 | 14 | 6 | 1 | 1 | 100 |

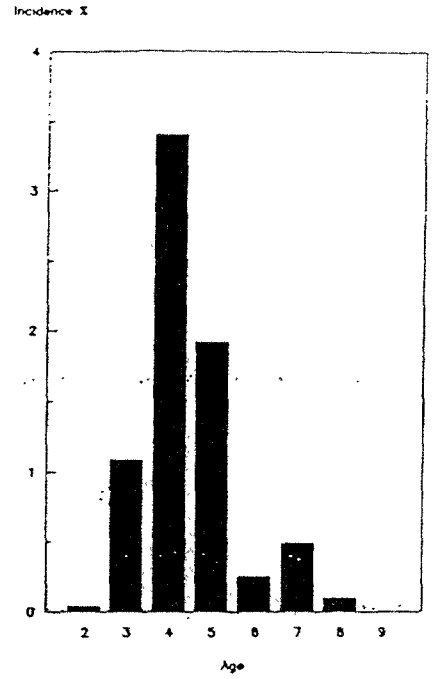


FIG 6: Age specific incidence of BSE cases in confirmed herds in 1987

No common factors, in terms of treatments to calves, young stock or the adult herd were present. These included the use of vaccines, hormones, organophosphorus fly sprays, synthetic pyrethroid sprays and ear tags and anthelmintics. There was no evidence of an association with any single compounder of proprietary feedstuffs, but all the affected animals for which an accurate feeding history was available had received proprietary feedstuffs.

Data on the use of weedkillers/herbicides and pesticides were obtained for the initial 145 farms. Weedkillers/herbicides had not been used on 22·9 per cent of farms and pesticides had not been used on 68·9 per cent of farms.

Analysis of the records of purchases of animals into affected herds over the previous seven years did not reveal any association between herds, except that three cases in purchased animals in three herds were from known affected herds.

The identities of the parents of 501 cases were available; 239 different sires were involved. BSE occurred in one of each of nine sets of female twins; seven cases were confirmed and

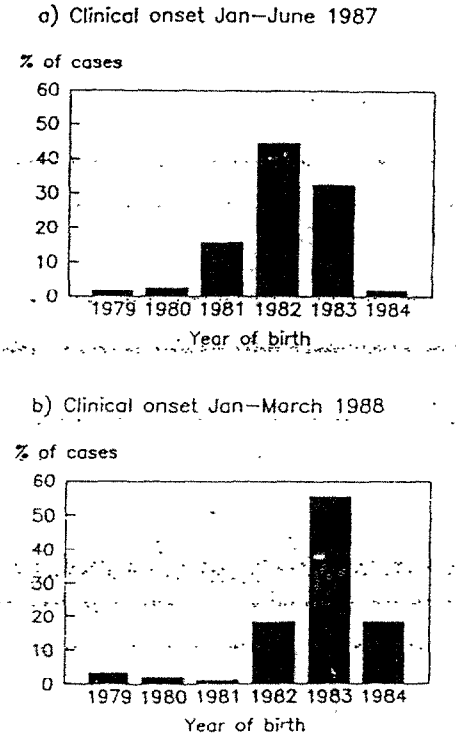


FIG 7: Percentage distribution of all BSE clinical cases by date of clinical onset and year of birth

TABLE 5: Distribution of 145 herds with at least one confirmed case by the presence of sheep on the farm and cattle purchasing policy since 1980

| Cattle purchasing policy since 1980 | Presence of sheep on farm since 1980 None | Own flock +/− winter grazing | Winter grazing only | Total |
|---|---|---|---|---|
| No purchases | 6 | 5 | 11 | 22 |
| No purchases, but bulls hired/shared | 1 | 3 | 3 | 7 |
| Breeding animals purchased | 22 | 49 | 45 | 116 |
| Total | 29 | 57 | 59 | 145 |

two were suspected clinically. All the unaffected twins survived to at least the age of their sibling except for the twin of one of the clinically suspect cases which was culled one year earlier.

Fifty-three confirmed cases, for which data were available to identify at least five generations in the sire line, were found in a search of the pedigree database for bulls which were common to at least 10 cases. Irrespective of the relationship between the bulls so identified, the maximum number of cases related to one bull was 26.

Two hundred and seventy-nine female offspring with both a putative carrier sire and maternal grandsire were identified from the breeding records of the one herd. The distribution of these offspring by their year of birth, their maximum age attained in the herd up to June 1987, and BSE status is shown in Table 6. There was no evidence in these data of the anticipated segregation ratio of seven unaffected animals : one confirmed case to support the hypothesis of an autosomal recessive inheritance of BSE.

The use of a computer based simulation model indicated that the values of the age specific incidences observed in 1987 were consistent with the following features. First, both calves and adults (over two years old) have been exposed, but the risk of exposure for calves was 30 times that for adults; secondly, exposure of the cattle population commenced in the winter of 1981/1982 and continued to at least the end of 1984 and, thirdly, an incubation period with a range from 2·5 years to at least eight years and a log normal distribution. The maximum incubation period that could have been observed in 1987 was six years. Further epidemiological data for 1988 and subsequent years is needed to determine whether exposure continued after 1984.

If exposure is assumed to have continued, but with no change in the risk of exposure, such as that from cattle to cattle transmission, then the annual incidence rates in three- and four-year-old animals would remain constant, and those in the older age groups would increase slightly over the next two to three years and then stabilise at a lower rate than in the three- and four-year-old age groups. This would result essentially in a constant incidence of cases.

## Discussion

The results of this study support and extend the original (Wells and others 1987) and subsequent evidence (Hope and others 1988) of a close relationship between BSE and the transmissible spongiform encephalopathies caused by unconventional infectious agents.

Presenting signs given in herd histories provide useful indicators of the initial perceptions of the disorder by herdsmen, but as they were determined by the opportunities for observation in relation to herd management they may not give a true picture of the onset of disease. Interpretation of a clinical neurological basis for the reported clinical signs was also necessarily limited by the form of the data and may require revision with more detailed studies of the clinical progression of the disease. The constellation of neurological signs ultimately apparent in the majority of cases included behavioural disorders, gait ataxia, paresis and loss of bodyweight (see also Cranwell and others 1988, Whitaker and Johnson 1988) and is consistent with a diffuse central nervous system disorder. The most obvious difference between the clinical signs in BSE and in scrapie was that in BSE pruritus was not a predominant sign. The frequency of clinical signs gave a perspective of the clinical syndrome but as in scrapie and other transmissible spongiform encephalopathies, with the exception of kuru (Hornabrook 1979), the presenting clinical signs and the disease course of BSE showed considerable variation.

The initial changes in behaviour, in a high proportion of cases, were suggestive of hypomagnesaemia or nervous ketosis. A lack of response to treatment and the more insidious onset of the clinical signs and their chronicity are of value in differentiating BSE from these two conditions. Cases of listeriosis, diagnosed histopathologically during the course of this study, which had clinical signs suggestive of BSE had a considerably shorter clinical course, of 15 days or less, before euthanasia became necessary, compared with the majority of confirmed cases of BSE. Other differential diagnoses which may need to be considered include lead poisoning, cerebrospinal abscesses or other space occupying lesions and spinal trauma. Clinical blood biochemistry has not revealed consistent abnormalities in confirmed cases of BSE (Johnson and Whitaker 1988, Whitaker and Johnson 1988).

The recorded distribution of the duration of the illness was confounded by the euthanasia of animals, but is similar to that observed in natural scrapie of sheep (Dickinson 1976, Palsson 1979), chronic wasting disease of captive mule deer (*Odocoileus hemionus hemionus*) (Williams and Young 1980), spongiform encephalopathy of Rocky Mountain elk (*Cervus elaphus nelsoni*) (Williams and Young 1982) and Creutzfeldt-Jakob disease of man (Bernoulli and others 1979, Malmgren and others 1979). Cases with a duration of clinical illness of less than 15 days were associated with an acute onset of clinical signs. Similar clinical histories have been observed in cases of scrapie in sheep (Joubert and others 1972) and of Creutzfeldt-Jakob disease in man (Bernoulli and others 1979). Since re-

TABLE 6: Distribution of female offspring born in one herd, with a putative carrier sire and maternal grandsire, by year of birth and number of months surviving in the herd

| Maximum age in herd up to June 1987 (months) | Year of birth 1975 | 1976 | 1977 | 1978 | 1979 | 1980 | 1981 | 1982 | 1983 | 1984 | 1985 | 1986 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ≤12 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 7 | 9 |
| 13-24 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 65 | 1 | 69 |
| 25-36 | 0 | 0 | 3 | 1 | 4 | 0 | 12 | 7 | 10 | 12 | 1 | 0 | 50 |
| 37-48 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 8 | 15 | 3 | 0 | 0 | 29 |
| 49-60 | 1 | 0 | 0 | 0 | 6 | 1 | 3(1) | 23(3) | 6 | 0 | 0 | 0 | 40 |
| 61-72 | 0 | 0 | 0 | 0 | 0 | 1 | 22(1) | 9 | 0 | 0 | 0 | 0 | 32 |
| 73-84 | 0 | 0 | 0 | 2 | 2 | 12 | 3 | 0 | 0 | 0 | 0 | 0 | 19 |
| 85-96 | 0 | 0 | 0 | 2 | 11 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 16 |
| 97-108 | 0 | 0 | 0 | 3 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 8 |
| ≥ 109 | 2 | 0 | 3 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 7 |
| Total | 3 | 1 | 6 | 11 | 30 | 18 | 40 | 47 | 32 | 17 | 66 | 8 | 279 |

Numbers in brackets are numbers of confirmed cases of BSE

cumbency was the culminating feature of five of the seven short duration cases, cows which present with 'downer cow syndrome' should also be considered potential, if atypical, cases of BSE.

The preponderance in the Friesian and Friesian-Holstein breeds precluded any quantitative comparison of the clinical history and signs in the various breeds affected, but there were no obvious major differences between breeds.

This study sustains the premise that BSE is a novel disease in cattle with the first clinically suspect cases occurring in April 1985. While the possibility that sporadic cases occurred at a very low incidence before April 1985 cannot be dismissed, it must be emphasised that the initial annual incidence detected was of the order of one case per 100,000 adult animals. Bovine spongiform encephalopathy has not been reported in any other country, but Marsh and Hartsough (1986, 1988) have reported that they suspect a scrapie-like disease of cattle in the USA.

The hypothesis of the introduction of a novel infectious agent through a particular biological product was not supported by the use of such products in affected herds. The absence also of any a association between the time of onset of clinical signs and either the calendar month or stage of pregnancy was not consistent with an acute toxic effect of pharmaceutical products or agricultural chemicals, the uses of which are restricted to particular months or seasons, or to specific times in an animal's life span or production cycle.

In scrapie, the role of genetics is now generally considered to be involved in the determination of susceptibility to disease (Dickinson and others 1968, Foster and Dickinson 1988). Previously, it had been proposed that genetics had a role in determining directly the expression of scrapie through an autosomal recessive mode of inheritance (Parry 1962). The number of sires of cases involved and the absence of any breed association militated against an autosomal mode of inheritance as a cause of BSE and the specific genetic analysis in the one herd further eliminated the possibility of BSE being exclusively determined by simple mendelian inheritance. The precise role of genetics in determining susceptibility to BSE remains unknown, but is a subject of further research.

The analysis of the records of purchases of animals and the investigation of the pedigrees of the sires used, particularly in closed herds, provided conclusive evidence that BSE was not introduced into Great Britain by imported cattle or disseminated via semen.

The distribution of cases by month and year of onset, is characteristic of an extended common source epidemic. Movement of cattle between known affected herds could not account for the occurrence of cases within and between herds. No evidence of cattle to cattle transmission was found; all affected animals therefore appeared to be index cases.

There is pathological evidence that the aetiology of BSE is related to that of scrapie. In addition to the light microscopic similarities, electron microscopical examination of extracts of fresh brain from confirmed cases of BSE have detected scrapie associated fibrils (Wells and others 1987, Wells and Scott 1988) the occurrence of which is confined to spongiform encephalopathies associated with transmissible agents (Merz and others 1983). More recently, molecular studies of brain fibrils from confirmed cases of BSE have substantiated the scrapie-like nature of BSE (Hope and others 1988).

The results of the present study preclude the transmission of the scrapie agent from sheep to cattle via direct or indirect contact on affected farms because of the form of the epidemic and the absence of sheep on 20 per cent of farms with BSE. The results of the study do, however, lead inevitably to the conclusion that cattle have been exposed to a transmissible agent via cattle feedstuffs.

The occurrence of a transmissible spongiform encephalopathy (TME) in ranch reared mink (*Mustela vison*) first recorded 40 years ago (Hartsough and Burger 1965) is a probable precedent for the food-borne transmission of the scrapie agent. A source of the infection in mink has been attributed to the feeding of scrapie infected sheep or goat tissues (Marsh and Hanson 1979).

Commercial concentrates, either as finished rations such as pelleted calf feed and dairy cow cake, or protein supplements used in home mixed rations, were fed at some time to all the cases for which accurate records were available. Two animal-derived products, meat and bone meal, and tallow, may be incorporated into these feedstuffs. Studies are in progress to determine more precisely the exposure of affected and unaffected animals to meat and bone meal in commercial concentrates, but the current evidence suggests that meat and bone meal has been the vehicle of infection. Meat and bone meal is distributed, and incorporated into animal rations, within a relatively small radius of its production compared with tallow (MMC 1985). The geographical variation in incidence is not consistent with the distribution and use of tallow. Also, scrapie-like agents are intimately associated with cell membranes (Millson and others 1976) and in the rendering process such agents would probably partition with the cellular residues of the meat and bone meal fraction, rather than with the lipids of tallow.

The food-borne hypothesis is also supported by the considerably greater incidence in dairy herds compared with beef suckler herds, because there is less concentrate feeding, particularly of calves, in the latter herd type. The positive association between herd size and the risk of occurrence of a case of BSE is likely to be due to an increased probability of purchasing an infected batch of food with increasing herd size. It is also interesting in this respect to note the occurrence of a scrapie-like disorder with spongiform encephalopathy in a 33-month-old nyala (*Tragelaphus angasi*) in 1986 and in a gemsbok (*Oryx gazella*) in 1987 on a wildlife park in the south of England (Anon 1986, Jeffrey and Wells 1988). These animals had no contact with each other and no source of a transmissible agent was evident when they were investigated. Further investigations revealed that they were fed a concentrate ration containing meat and bone meal. This ingredient was first incorporated into the ration in early 1986 and the maximum incubation period was three months for the nyala and 15 months for the gemsbok.

There was no clear or single explanation why, in 1982, cattle apparently became first exposed to a transmissible agent sufficiently to result in clinical disease. A number of factors have been identified which when combined are undoubtedly significant in the occurrence of this epidemiological phenomenon. These include: a dramatic increase in the sheep population in Great Britain which commenced in 1980 and has continued (MAFF 1988); a probable increase in the prevalence of scrapie infected flocks (J. W. Wilesmith unpublished data); the greater inclusion of sheep heads in material for rendering; the greater inclusion of casualty and condemned sheep in material for rendering as a result of the reduction in the number of knackers' yards; the introduction of continuous rendering processes during the 1970s and 1980s which may have resulted in the rendering of animal material at a lower temperature and, or, a shorter time than previously and the decline in the practice of using hydrocarbon solvents and terminal heat treatment for fat extraction since the mid 1970s (MMC 1985).

These factors provide a possible explanation for a change in the exposure of cattle to sheep-derived protein and the scrapie agent. A further hypothesis to explain the occurrence of BSE is the emergence or selection of a strain, or strains, of the scrapie agent pathogenic for cattle. Mutations of the scrapie agent, which can be selected after a single passage in mice, have been well documented (Bruce and Dickinson 1979). If BSE was the result of a localised chance transmission from sheep to cattle of a mutant scrapie strain (or strain giving rise to a mutant) an increasing incidence over time would be expected. This is not the case. The form of the epidemic and the geographically widespread occurrence of BSE would require the simultaneous emergence of this mutant scrapie strain in a large number of flocks (or cattle herds) throughout the country

The reason for the geographical variation in incidence was not established by this study. The variation could not be explained simply either by the variation in the potential exposure of cattle to sheep material in the south of England compared to other regions (J. W. Wilesmith unpublished data) or by a geographical variation in dairy herd size distribution. Studies are in progress to attempt to explain the geographical variation in incidence. One hypothesis is that it mirrors the geographical variation in the market share of cattle feedstuffs between the compounders and assumes that there is a variation between companies in the use and inclusion rate of meat and bone meal.

The higher risk of infection for calves, compared with adults, as assessed by computer modelling, is consistent with the findings in a high proportion of multiple incident herds in which BSE cases were restricted to one age cohort. The relatively low mean annual within herd incidence therefore understates the true incidence in the putatively exposed animals. The higher risk of exposure for calves could be due to a difference in susceptibility with age and, or, the dose of agent received.

The age specific incidences were similar to those observed for natural scrapie in sheep (Dickinson 1976). In scrapie, this is undoubtedly due to the high component of maternal transmission of infection and a comparable incubation period, but it does not necessarily imply the occurrence of maternal transmission of BSE. Insufficient time has elapsed to determine whether maternal transmission (prenatally and, or, perinatally) occurs in BSE and if so, at what incidence. This is the subject of the continuation of the present study, but given the ages of the BSE cases, and therefore the number of their offspring which will survive the minimum incubation period, the occurrence of maternal transmission would not be expected to have an effect on the annual incidence until at least 1990.

There was no evidence that the exposure of the cattle population was for a discrete short period or that it ceased at the end of 1984. However, if exposure did cease in 1984, then from 1988 the incidence would begin to decline, becoming insignificant in 1991 and effectively zero in 1994, assuming that cattle to cattle transmission does not occur. If exposure continued after 1984 then the introduction of EEC milk quotas in 1984, which resulted in lower rates of concentrate feeding to dairy cows, may produce a slight reduction in incidence. The effect of the inclusion of infected cattle into the cattle food chain, via the rendering system, is difficult to quantify, but a slight increase in incidence could be expected. Assuming the summation of these effects is minimal and the exposure has continued beyond 1984, the annual incidence is likely to continue at a constant rate, of the order of two cases per 10,000 adult cows per year, until 1990 when the effect of any vertical transmission may be revealed.

The effect of the recently introduced (July 1988) suspension of the inclusion of ruminant-derived animal protein in ruminant feedstuffs (Order 1988) on the incidence will be determined by the continuation of the present study. A resultant reduction in incidence is not expected until 1992.

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## Addendum

The recent preliminary report (Fraser and others 1988) of production of scrapie-like disease in mice inoculated with brain homogenates from BSE cases provides the first direct evidence that BSE is a transmissible disease.

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